DEPARTMENT OF HEALTH & HUMAN SERVICES PUBLIC HEALTH SERVICE

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852

Division of Clinical Trial Design and Analysis
HFM-576

Date: 11/4/97

From: M.Walton, DCTDA

Subject: Supervisory Overview of BLA 97-0202

To: File BLA 97-0202

Background

Abciximab (ReoPro©) is the Fab fragment of the chimeric monoclonal antibody c7E3 which binds to platelets and inhibits aggregation. Abciximab received initial marketing approval in 1994 for use as an adjunct during percutaneous transluminal coronary angioplasty (PTCA, now more broadly referred to as percutaneous coronary interventions, PCI) in patients believed to be at high risk for abrupt artery closure for the prevention of cardiac ischemic events. This was based upon the EPIC trial, which showed improved outcome on the incidence of the three-part-composite event endpoint of death, myocardial infarction or urgent reintervention within thirty days of PTCA. However, this was associated with increased rates of clinically significant bleeding in the abciximab treated patients. Due to the increased rate of bleeding, an important phase 4 commitment made at the time of marketing approval was to study means of decreasing the bleeding associated with the use of abciximab.

Based upon the manner of usage studied in the EPIC trial abciximab is recommended to be administered as a bolus shortly prior to initiating the PTCA, followed by a 12 hour infusion. Abciximab was studied only with a single specified concomitant regimen of aspirin and heparin, and all safety and efficacy information is in the setting of that concomitant regimen.

This BLA Supplement focuses upon a subsequent trial, CAPTURE that investigated a different administration regimen in the setting of unstable angina not responding to conventional medical therapies. Dr. Rieves has performed the clinical review of these data. This memorandum summarizes and comments upon the submission based upon Dr. Rieves's review, which should be referred to for full details.

Design of the CAPTURE Study

The CAPTURE Study was a randomized, double-blind, placebo controlled phase 3 study conducted in 69 sites primarily in Europe. The objective was to assess the safety and efficacy of abciximab when administered to unstable angina patients who are not responding to conventional medical therapies and are scheduled for PTCA within 18 to 24 hours. The protocol's statement of

objectives included comparing a) episodes of new ischemia prior to the PTCA, b) ischemic complication rates within 30 days following the PTCA, and c) rates of ischemic events within 6 months following PTCA. These objectives, however, were not all clearly incorporated into the analytic plan of the study.

The study enrolled patients with unstable angina who did not adequately respond to at least two hours of conventional therapies (e.g. bed rest, nitrates, heparin) and who had a screening angiogram demonstrating a culprit lesion suitable for PTCA. The PTCA was scheduled for 18 to 24 hours following randomization to one of two groups. The two treatment groups were placebo or abciximab administered as a bolus of 0.25mg/kg followed by a 10 μg/min infusion for 18 to 26 hours, terminating 1 hour after the PTCA. Heparin was administered during the pre-PTCA infusion as well as during the PTCA period, and for at least 1 hour following the PTCA. All patients were-also treated with aspirin. A notable aspect of the treatment protocol is that the management is different from the patient management guidelines instituted in the EPILOG trial of companion BLA 97-0200.

The study's primary endpoint was the rate of occurrence of a composite event of death, MI, or urgent intervention within 30 days following the PTCA. The secondary endpoints of the analytic plan were complex and multiple. An apparent set of most important secondary endpoints consisted of comparing between treatment groups the rate of each of the primary endpoint event components (mortality, MI, and urgent intervention taken individually) during the separate time periods of randomization to PTCA, and from PTCA to day 30. Although a stated objective of the study, analysis of the 6 month outcome was not listed high in the priority order of the secondary endpoints.

While planned for 1400 patients, a prospectively planned interim analysis that examined 1050 patients determined that adequate evidence for early termination due to efficacy was seen, and the study was terminated early. A total of 1267 patients had been enrolled by study termination. Most patients were administered the planned regimen, blinding was well maintained, the treatment groups were similar with regards to major demographic and disease characteristics, and nearly all patients received PTCA at approximately the planned time.

CAPTURE Study Results

The intent to treat analysis of the primary endpoint showed improved outcome associated with the abciximab treatment. The composite endpoint event rate was 15.9% in the placebo group while there were 11.3% of the abciximab group with an endpoint event ($p=0.012$, logrank test).

The comparisons of the individual event types in the two time periods for the secondary endpoint analyses showed that mortality was not different between the groups in either time period, the rates of MI were reduced in the abciximab group vs. placebo in both time periods, and the rate of urgent intervention was also reduced in the abciximab group in the post-PTCA period. As earlier-than-planned initial PTCA was excluded as an "urgent revascularization" event, there was little power to detect differences between groups in this component in the period prior to the initial PTCA.

The six month outcome was the comparison of rates of occurrence of the composite endpoint event of mortality, MI, or any revascularization intervention. This endpoint showed no difference between the two treatment groups (3 1% both groups).

The safety analysis raised no new concerns for adverse events related to abciximab. The primary concerns were of hemorrhage and thrombocytopenia. There was a modest increase in hemorrhage associated with the use of abciximab, most of which is bleeding from the femoral access site. Classified by the TIM1 criteria for bleeding severity, there were 3.8% of abciximab patients with major bleeding (not related to CABG), vs. 1.9% of placebo patients, and 4.8% of abciximab patients with minor bleeding not related to CABG, vs. 2.0% of placebo patients. Rates of RBC transfusion also reflected a higher incidence of important bleeding in the abciximab group. The rates of bleeding seen in the CAPTURE study were less than that seen in the EPIC study, but higher than that seen in the EPILOG study in the companion BLA 97-0200.

The incidence of thrombocytopenia (counts < 100,000) was different between the two groups, with an incidence in the abciximab group of 5.6%, similar to the 5.2% previously seen in the EPIC study (vs. 1.3% in the placebo group). Incidence of platelet counts < 50000 and of platelet transfusions were similarly increased in the abciximab group, but also consistent with those seen in the EPIC and EPILOG studies.

Conclusions

The CAPTURE study has evaluated a carefully defined subset of unstable angina patients, characterized by being unresponsive to at least 2 hours of conventional medical therapies (bed rest, nitrates, heparin) and planned for PTCA to be definitely performed within 24 hours (due to angiographic demonstration of a lesion suitable for PTCA). In this subset of patients CAPTURE has shown that abciximab can decrease the rate of acute cardiac ischemic complications occurring within 30 days following the PTCA. The regimen of abciximab used in this setting is different than that used in the current labeling (primarily a 24 hour infusion prior to PTCA vs. a 12 hour infusion following PTCA).

This does not constitute a truly new indication for abciximab. Abciximab's use in this manner is still focussed upon it's use as an adjunct to PTCA, and abciximab's benefit remains primarily reducing the incidence of ischemic complications that are seen to follow the PTCA. Because the majority of abciximab benefit occurs during or shortly following PTCA, the performance of a PTCA appears to be a critical event for abciximab efficacy. PTCA may induce much of the ischemic complications, thereby providing opportunity for abciximab's benefit in reducing these complications. The previous EPIC trial and the companion BLA's EPILOG trial also showed that the majority of the reduction in complications occurs within the 48 hours following PTCA.

Abciximab's benefit in the pre-PTCA period is suggested by the decreased rate of MI seen in that period during this study. However, this evidence is insufficient to establish a claim of benefit for abciximab in unstable angina prior to, or in the absence of, PTCA.

Of particular note is the lack of benefit seen in the 6 month endpoint. The importance of this "catch-up" is not clear. The 30 endpoint includes urgent intervention as a component, while the 6 month endpoint includes any intervention. This decline in efficacy by the 6 month time point

is reflected in the results of other abciximab trials as well. The EPILOG study also shows a lessened difference between treatment groups on the 6 month endpoint using any re-intervention compared to the 30 day endpoint.

No new safety concerns were raised by the CAPTURE study. Bleeding associated with abciximab was reduced from the levels seen during the EPIC trial, but were not as low as those seen during the EPILOG trial. There were several different aspects to the patient management guidelines between the CAPTURE and EPILOG trials. However the regimens are also very different, and not all the EPILOG guidelines may be transferable to this setting and regimen.

Recommendations

I concur with Dr. Rieves in his recommendations regarding this BLA Supplement.

The regimen studied in the CAPTURE trial can be recommended for the subset of unstable angina patients in whom it was investigated, patients not responding to conventional medical therapy in whom PTCA is planned to occur within 24 hours.

This recommendation in effect provides for an alternative regimen under the current indication for a particular subset of indicated patients. The general formulation that abciximab is indicated as an adjunct to PTCA remains accurate.

Extension of this claim to patients not meeting this criteria of refractory unstable angina, or not planned for PTCA within 24 hours is unwarranted at this time. However, incorporating a screening angiogram into the labeling for this regimen is not warranted; other methods deemed suitable by a physician for determining which patients will receive PTCA within a 24 hour period are likely to provide similar effects.

The regimen studied (infusion for 18 to 24 hours prior to PTCA, and concluding 1 hour post-PTCA) should be the regimen recommended in the labeling. An altered regimen, such as combining both the pre-PTCA 24 hour infusion with the post-PTCA 12 infusion has not been studied, and should not be recommended.

The safety results seen in the CAPTURE study should be clearly provided in labeling and promotional materials to enable evaluation of the safety of this regimen. The regimens used in CAPTURE and EPILOG are markedly different, and not all of EPILOG's management guidelines may be transferrable to this setting. Consequently, the bleeding rates seen in EPILOG may not be relevant to this manner of abciximab usage.